Original paper

Is there any increased risk of hypertension, diabetes and cardiac diseases in psoriatic patients with TNF-α G238A and G308A polymorphism?

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Abstract

Introduction: Psoriasis is regarded as a complex autoimmune disease with strong genetic background. Psoriatic patients suffer from many comorbidities including hypertension, diabetes and cardiovascular diseases. Cytokines such as tumor necrosis factor α (TNF-α) may be a key player that triggers psoriasis and diabetes, hypertension and cardiac disease at the same time.

Aim: To evaluate genetic variations in the TNF-α region and its association with psoriasis and related comorbidities.

Material and methods: The study covered 129 psoriasis patients with three main subgroups with coronary artery disease (n = 41), hypertension (n = 35), and diabetes (n = 21). DNA samples were genotyped for TNF-α G308A and G238A polymorphisms by real-time polymerase chain reaction melting-curve analysis and results were compared statistically.

Results: Psoriatic patients with both TNF-α-298 and TNF-α-308 polymorphisms showed no statistically significant increase in the risk of hypertension (OR = 0.425, χ^2 = 1.76, p = 0.18 and OR = 1.87, χ^2 = 1.33, p = 0.25), coronary artery disease (OR = 1.97, χ^2 = 1.91, p = 0.17 and OR = 2.63, χ^2 = 1.35, p = 0.25), or diabetes (OR = 1.35, χ^2 = 0.24, p = 0.62 and OR = 1.53, χ^2 = 0.24, p = 0.62).

Conclusions: The current preliminary results suggested that there was no correlation between TNF-α promoter polymorphism and diabetes, hypertension and cardiac disease among psoriatic patients in the Turkish population.

Key words: psoriasis, diabetes, hypertension, tumor necrosis factor α, G298A, G308A.

Introduction

Psoriasis is a common inflammatory skin disease affecting 1–3% of the population [1]. It is accepted not only as a skin disease but also a multisystemic disorder having a risk of comorbidities such as hypertension, diabetes, cardiovascular disorders, metabolic syndrome, etc. [2, 3]. The aetiopathogenesis of the psoriasis is still unclear hence immunogenetic studies are required to explain the underlying mechanisms.

Tumour necrosis factor α (TNF-α) is an important proinflammatory cytokine that plays a role in the pathogenesis of several diseases such as psoriasis, diabetes, cardiovascular disease and cancer [4–9]. It is located in the major histocompatibility complex III (MHC) region on chromosome 6p21.3. TNF-α gene includes various common single nucleotide polymorphisms (SNP) like –238 (rs361525), –308 (rs1800629), and –857 (rs1799724) positions. Today it is known that TNF-α polymorphisms are related with the occurrence of the psoriasis [10–12]. Besides psoriasis, TNF-α 308 and TNF-α-238 locus (G→A) mutation within the TNF-α gene promoter region is also found relevant in hypertension and cardiovascular disease [13].

In this study, we evaluated the metabolic and cardiovascular involvement in the presence of TNF-α-238 G/A and TNF-α-308 G/A polymorphisms in psoriatic patients.

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Aim

The aim of this study was to investigate whether TNF-α-238 G/A and TNF-α-308 G/A polymorphisms are valuable to define the risk of diabetes, hypertension and cardiac diseases in patients with psoriasis or not.

Material and methods

A total of 129 psoriatic patients were recruited to the study at the outpatient clinics of the Dermatology Department of Çanakkale Onsekiz Mart University (Turkey). All the patients were checked up by a cardiologist and an internal medicine specialist at least once. For the purpose of the study, the psoriatic patients were grouped into three main subgroups with coronary artery disease (CAD, $n = 41$), hypertension ($n = 35$), and diabetes ($n = 21$). Demographic characteristics of the patients are shown in Table 1. All participants signed informed consent before joining the study. The study protocol was approved by the Local Ethical Committee of Çanakkale Onsekiz Mart University. During the study, the Declaration of Helsinki principles were followed.

The peripheral blood samples of 129 psoriatic patients were collected and stored in ethylenediaminetetraacetic acid (EDTA) containing tubes. The genomic DNA extraction was performed by High Pure PCR Template preparation Kit (Roche, Germany) according to the manufacturer's instructions and kept at –80°C until real time polymerase chain reaction (RT-PCR). Gene amplification was performed by RT-PCR using specific primers and probes belonging to the TNF-α promoter region polymorphism (TNF-α-238 G/A and TNF-α-308 G/A).

The reaction was performed in a total of 20 µl of final reaction volume with 5 µl genomic DNA (approximately 50 ng DNA), 7.4 µl PCR-grade fluid, 1.6 µl Mg^{2+} solution (4 mM Mg^{2+}), 4 µl of primer and probe mixture, and 2 µl Roche Light Cycler Fast Start DNA Master (Roche Applied Science).

The determination of single nucleotide polymorphisms was carried out (Roche LightCycler) under the following conditions: initial denaturation step at 95°C for 10 min, then 40 cycles at 95°C for 10 s, 10 s at 60°C and 15 s at 72°C, dissolution-melting at 95°C for 20 s, at 40°C for 20 s and 0.2 continuous mode at 85°C, and cooling at 40°C for 30 s. All PCR conditions were performed under universal PCR conditions indicated above for the TNF-α/rs1800629 and TNF-α/rs361525 polymorphic sites. Non-mutated 298G/G allele (wild) was evaluated in 530 channel at a Tm of 58°C, whereas mutated 298A/A allele was evaluated again in the same channel at 65°C Tm. Also wild allele 308A/A and mutated allele 308G/G were evaluated in 530 channel at a Tm of 65°C and 54°C in 530 channel, respectively.

Statistical analysis

Statistical analysis of data was performed using 19.0 version of SPSS package program. The frequencies of alleles and genotypes of TNF-α at positions 308 and 238 were evaluated by allele counting methods. The comparison of the allele and genotype frequencies between groups and examination of the deviation of genotype distribution from Hardy Weinberg equilibrium were checked by χ^2 test. The odds ratio (OR) was used to estimate the risk of each disease (diabetes, hypertension and cardiovascular disease) depending on the presence of the variant allele or genotypes among psoriatic patients.

Results

Table 1 shows the baseline characteristics of the study population. The correlation of TNF-α promoter polymorphisms was examined by comparing psoriatic patients with comorbidities with a non-comorbid group.

The relationship between TNF-α G238A and G308A gene genotypes and hypertension is shown in Table 2. The genotype frequencies for the TNF G238A in the hypertensive psoriatic group and non-hypertensive psoriatic group were in Hardy-Weinberg equilibrium ($p > 0.05$). On the other hand, we could not observe Hardy-Weinberg equilibrium for TNF G308A in non-hypertensive psoriatic patients ($p = 0.049$). There was not a significant difference of TNF-α G238A polymorphism between psoriatic patients with and without hypertension. Thus, the G238A polymorphism seems to be irrelevant as regards hypertensive psoriatic patients.

Table 1. Demographic features of patients with psoriasis

Variables	Psoriasis patients ($N = 129$)	
	n	%
	Mean ± SD	Median (min.–max.)
Age [years]	44.71 ±14.14	45.00 (18–80)
Psoriasis duration [years]	14.96 ±1.34	14.96 (0–59)
PASI score	7.82 ±6.142	6.00 (0–42)
Psoriasis onset age [years]	30.65 ±17.18	25.50 (0–76)
Family history of psoriasis:		
Present	32	24.81
Absent	97	75.19
Diabetes:		
Present	21	16.28
Absent	108	83.72
Hypertension:		
Present	35	27.13
Absent	94	72.87
Coronary artery disease:		
Present	41	31.78
Absent	88	68.22

Table 2. Distributions of genotype and carriage rate of TNF-α promotor region polymorphisms (G238A and G308A) and association analyses of polymorphisms with hypertension among psoriasis patients

SNP	Tests for deviation from Hardy-Weinberg equilibrium		Tests for association (CI: 95% confidence interval)				
	Psoriasis patients without hypertension	**Psoriasis patients with hypertension**	**Allele freq. difference**	**Heterozygous**	**Homozygous**	**Allele positivity**	**Armitage's trend test**
TNFG238A	nGG = 77 (77.77) nGA = 17 (15.46) nAA = 0 (0.77) f_a1 = 0.91 ±0.020 *F* = –0.09 *p* = 0.34 (Pearson) *p* = 0.19 (Llr) *p* = 1.00 (Exact)	nGG = 32 (32.06) nGA = 3 (2.87) nAA = 0 (0.06) f_a1 = 0.96 ±0.024 *F* = –0.045 *p* = 0.79 (Pearson) *p* = 0.71 (Llr) *p* = 1.00 (Exact)	Risk allele A [G]<->[A] Odds ratio = 0.450 CI: 0.128–1.587 χ^2 = 1.61 *p* = 0.20 (P)	[GG]<->[AG] Odds ratio = 0.425 CI: 0.116–1.550 χ^2 = 1.76 *p* = 0.18	[GG+]<->[AA] Odds ratio = 2.385 CI: 0.046–A2.769 χ^2 = NA *p* = 1.00	[AA]<->[GA + AA] Odds ratio = 0.425 CI: 0.116–1.550 χ^2 = 1.76 *p* = 0.18	Common odds ratio Odds ratio = 0.425 χ^2 = 1.76 *p* = 0.18
TNFG308A	nGG = 81 (79.60) nGA = 11 (13.80) nAA = 2 (0.60) f_a1 = 0.92 *F* = 0.20308 *p* = 0.048958 (Pearson) *p* = 0.10 (Llr) *p* = 0.096 (Exact)	nGG = 26 (26.58) nGA = 9 (7.84) nAA = 0 (0.58) f_a1 = 0.87 ±0.037 *F* = –0.15 *p* = 0.38 (Pearson) *p* = 0.25 (Llr) *p* = 1.005 (Exact)	Risk allele A [G]<->[A] Odds ratio = 1.702 CI: 0.708–4.088 χ^2 = 1.44 *p* = 0.23 (P)	[GG]<->[AG] Odds ratio = 2.549 CI: 0.951–6.829 χ^2 = 3.62 *p* = 0.057	[GG+]<->[AA] Odds ratio = 0.615 CI: 0.029–13.222 χ^2 = 0.64 *p* = 0.42	[AA]<->[GA + AA] Odds ratio = 2.157 CI: 0.828–5.621 χ^2 = 2.55 *p* = 0.11	Common odds ratio Odds ratio = 1.870 χ^2 = 1.33 *p* = 0.25

NA – not available.

In contrast, the risk of hypertension may be related with the TNFG308A polymorphism due to heterozygous genotype increased hypertension risk 2.5 times more in hypertensive psoriatic sub-groups (OR = 2.54; 95% CI: 0.95–6.82, *p* = 0.057).

As shown in Tables 3 and 4, the distribution of genotype and frequencies of the alleles of TNF-α G238A and G308A did not differ within the CAD and diabetes subgroups ($p > 0.05$). The results indicate that allele positivity in the TNF-α promoter region does not increase the CAD or diabetes risk among psoriasis patients (OR = 1.85, *p* = 0.19 and OR = 1.32, *p* = 0.55 for TNF-α G238A within CAD and diabetes subgroups and OR = 1.86, *p* = 0.006 and OR = 1.32, *p* = 0.55; for TNF-α G308A within CAD and diabetes subgroups). Overall odds ratio, heterozygous odds ratio and homozygous odds ratio are not correlated with the CAD or diabetes risk, either.

Discussion

Genetic studies are necessary to determine the risk of occurrence, clinical course and even the treatment options of the diseases. In recent years great progress has been achieved in the prognosis of psoriasis based on genetic researches. These studies emphasized that genetic factors affect the risk, age onset, clinical type and severity of psoriasis [14].

Growing evidence for psoriasis susceptibility genes from different research groups has shown that polymorphisms in different genes trigger psoriasis and also increase severity of psoriasis and psoriatic comorbidities [15–17]. Zhuang *et al.* and Zu *et al.* defined that TNF-α 308 G/A polymorphism decreases the psoriasis risk in contrast to TNF-α 238 G/A polymorphism increasing the risk of psoriasis. Magalhães *et al.* denoted a higher incidence of TNF-238 G/G genotype in severe psoriasis patients but they did not find TNF-α SNPs polymorphism significant in psoriatic patients. Jia *et al.* defined an increased risk of psoriasis for the 238G/A polymorphism and a reduced risk of psoriasis for the –308G/A polymorphism. On the other hand, TNF-α 238G/A and TNF-α 308 G/A polymorphisms are reported to be relevant to diabetes [18], CAD [19], and hypertension [5]. None of the studies have evaluated the link between TNF-α G238A and G308A polymorphisms and hypertension, CAD or diabetes among psoriasis patients. Therefore, we examined the relationship between TNF-α 238G/A and TNF-α 308G/A polymorphism and the risk of psoriatic comorbidities.

Neither the genotype nor allele frequencies of TNF-α/rs1800629 and TNF-α/rs361525 were statistically different between psoriatic patients with hypertension, CAD or diabetes and psoriatic patients with no comorbidity. The distribution of genotype frequencies for TNF-α G308A was inconsistent with Hardy-Weinberg expectations in psoriasis patients without hypertension (*p* = 0.049). On the contrary, the genotypes have Hardy-Weinberg equilibrium in TNF-α/rs1800629 and TNF-α/rs361525 in all other sub-groups. Our results revealed that TNF-α G308A polymorphisms may influence the risk of hypertension

Table 3. Distributions of genotype and carriage rate of TNF-α promotor region polymorphisms (G238A and G308A) and association analyses of polymorphisms with CAD among psoriasis patients

SNP	Tests for deviation from Hardy-Weinberg equilibrium		Tests for association (CI: 95% confidence interval)				
	Psoriasis patients without CAD	**Psoriasis patients with CAD**	**Allele freq. difference**	**Heterozygous**	**Homozygous**	**Allele positivity**	**Armitage's trend test**
TNFG238A	nGG = 77 (77.34) nGA = 11 (10.31) nAA = 0 (0.34) f_a1 = 0.94 ±0.018 *F* = –0.07 *p* = 0.53 (Pearson) *p* = 0.39 (Llr) *p* = 1.00 (Exact)	nGG = 32 (32.49) nGA = 9 (8.01) nAA = 0 (0.49) f_a1 = 0.89 ±0.032 *F* = –0.12329 *p* = 0.43 (Pearson) *p* = 0.29 (Llr) *p* = 1.00 (Exact)	Risk allele A				
			[G]<->[A]	[GG]<->[AG]	[GG+]<->[AA]	[AA]<->[GA + AA]	Common odds ratio
			Odds ratio = 1.849 CI: 0.735–4.654 χ^2 = 1.75 *p* = 0.19 (P)	Odds ratio = 1.969 CI: 0.744–5.207 χ^2 = 1.91 *p* = 0.17	Odds ratio = 2.385 CI: 0.046–122.769 χ^2 = NA *p* = 1.0	Odds ratio = 1.969 CI: 0.744–5.207 χ^2 = 1.91 *p* = 0.17	Odds ratio = 1.969 χ^2 = 1.91 *p* = 0.17
TNFG308A	nGG = 71 (70.03) nGA = 15 (16.95) nAA = 2 (1.03) f_a1 = 0.89 ±0.025 *F* = 0.11 *p* = 0.28 (Pearson) *p* = 0.32 (Llr) *p* = 0.25 (Exact)	nGG = 36 (36.15) nGA = 5 (4.70) nAA = 0 (0.15) f_a1 = 0.94 ±0.026 *F* = –0.06 *p* = 0.67 (Pearson) *p* = 0.56 (Llr) *p* = 1.00 (Exact)	Risk allele A				
			[G]<->[A]	[GG]<->[AG]	[GG+]<->[AA]	[AA]<->[GA + AA]	Common odds ratio
			Odds ratio = 1.86 CI: 0.671–5.180 χ^2 = 1.46 *p* = 0.22641	Odds ratio = 1.77 CI: 0.073–43.023 χ^2 = 0.65 *p* = 0.42	Odds ratio = 2.55 CI: 0.119–54.570 χ^2 = 1.00 *p* = 0.32	Odds ratio = 2.40 CI: 0.113–51.102 χ^2 = 0.95 *p* = 0.33	Odds ratio = 2.63 χ^2 = 1.35 *p* = 0.25

NA – not available.

among psoriatic patients, yet the results are slightly statistically significant. For that reason future studies are needed to examine the link between the TNF-α G308A polymorphisms and hypertension among psoriatic patients.

This is the first study that evaluates the risk of diabetes, hypertension and cardiovascular involvement of psoriatic patients and its association between TNF-α G238A and G308A polymorphisms. TNF-α gene promoter region polymorphisms (TNF-α-238 G/A and TNF-α-308 G/A) are

Table 4. Distributions of genotype and carriage rate of TNF-α promotor region polymorphisms (G238A and G308A) and association analyses of polymorphisms with diabetes among psoriasis patients

SNP	Tests for deviation from Hardy-Weinberg equilibrium		Tests for association (CI: 95% confidence interval)				
	Psoriasis patients without diabetes	**Psoriasis patients with diabetes**	**Allele freq. difference**	**Heterozygous**	**Homozygous**	**Allele positivity**	**Armitage's trend test**
TNFG238A	nGG = 92 (92.59) nGA = 16 (14.81) nAA = 0 (0.59) f_a1 = 0.93 ±0.017 *F* = –0.08 *p* = 0.41 (Pearson) *p* = 0.26 (Llr) *p* = 1.00 (Exact)	nGG = 17 (17.19) nGA = 4 (3.62) nAA = 0 (0.19) f_a1 = 0.90 ±0.043 *F* = –0.10526 *p* = 0.63 (Pearson) *p* = 0.52 (Llr) *p* = 1.00 (Exact)	Risk allele A				
			[G]<->[A]	[GG]<->[AG]	[GG+]<->[AA]	[AA]<->[GA + AA]	Common odds ratio
			Odds ratio = 1.316 CI: 0.417–4.152 χ^2 = 0.22 *p* = 0.55 (F)	Odds ratio = 1.353 CI: 0.403–4.545 χ^2 = 0.24 *p* = 0.62	Odds ratio = 5.286 CI: 0.101–275.364 χ^2 = NA *p* = 1.00	Odds ratio = 1.353 CI: 0.403–4.545 χ^2 = 0.24 *p* = 0.62	Odds ratio = 1.353 χ^2 = 0.24 *p* = 0.62
TNFG308A	nGG = 92 (92.59) nGA = 16 (14.81) nAA = 0 (0.59) f_a1 = 0.93 ±0.017 *F* = –0.08000 *p* = 0.41 (Pearson) *p* = 0.26 (Llr) *p* = 1.00 (Exact)	nGG = 17 (17.19) nGA = 4 (3.62) nAA = 0 (0.19) f_a1 = 0.90 ±0.043 *F* = –0.10526 *p* = 0.63 (Pearson) *p* = 0.52 (Llr) *p* = 1.00 (Exact)	Risk allele A				
			[G]<->[A]	[GG]<->[AG]	[GG+]<->[AA]	[AA]<->[GA + AA]	Common odds ratio
			Odds ratio = 1.316 CI: 0.417–4.152 χ^2 = 0.22 *p* = 0.55 (F)	Odds ratio = 1.353 CI: 0.403–4.545 χ^2 = 0.24 *p* = 0.62	Odds ratio = 5.286 CI: 0.101–275.364 χ^2 = NA *p* = 1.0	Odds ratio = 1.353 CI: 0.403–4.545 χ^2 = 0.24 *p* = 0.62	Odds ratio = 1.353 χ^2 = 0.24 *p* = 0.62

NA – not available.

associated with hypertension and cardiovascular disease in different studies, yet these polymorphic regions did not directly increase the risk of comorbidities among psoriatic patients. We think that the superiority of our study is to show if we can identify the risk of comorbidities like hypertension, cardiovascular diseases or diabetes accompanying psoriasis using the TNF-α promoter region polymorphisms. But consistently with the literature, our results showed that genetic studies are important but are not the only solution for the disease.

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Conflict of interest

The authors declare no conflict of interest.

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